(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 October 2008 (23.10.2008)

PCT

(10) International Publication Number
WO 2008/127314 A1

(51) International Patent Classification:
G01N 27/414 (2006.01)

(21) International Application Number:
PCT/US2007/024126

(22) International Filing Date:
19 November 2007 (19.11.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/860,586 22 November 2006 (22.11.2006) US

(71) Applicant *(for all designated States except US)*: PRESIDENT AND FELLOWS OF HARVARD COLLEGE [US/US]; 17 Quincy Street, Cambridge, MA 02138 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: LIEBER, Charles, M. [US/US]; 27 Hayes Avenue, Lexington, MA 02173 (US). GAO, Xuan, P.a. [CN/US]; 9 Fayette Street, Apt. #1, Cambridge, MA 02139 (US). ZHENG, Gengfeng [CN/US]; 227 Centre Street, Apt. #2, Dorchester, MA 02124 (US).

(74) Agent: OYER, Timothy, J.; Wolf, Greenfield & Sacks, P.C., Federal Reserve Plaza, 600 Atlantic Avenue, Boston, MA 02210-2206 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(54) Title: HIGH-SENSITIVITY NANOSCALE WIRE SENSORS

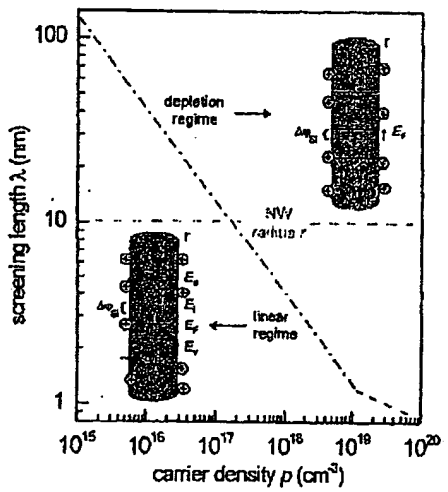

Figure 1

(57) Abstract: The present invention generally relates to nanoscale wire devices and methods for use in determining analytes suspected to be present in a sample. The invention provides a nanoscale wire that has improved sensitivity, as the carrier concentration in the wire is controlled by an external gate voltage, such that the nanoscale wire has a Debye screening length that is greater than the average cross- sectional dimension of the nanoscale wire when the nanoscale wire is exposed to a solution suspected of containing an analyte. This Debye screening length (lambda) associated with the carrier concentration (p) inside nanoscale wire is adjusted by adjusting the gate voltage applied to an FET structure, such that the carriers in the nanoscale wire are depleted.

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HIGH-SENSITIVITY NANOSCALE WIRE SENSORS

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/860,586, filed November 22, 2006, entitled "High-Sensitivity Nanowire Sensors," by Lieber, *et al.*, incorporated herein by reference.

FIELD OF INVENTION

Various aspects of the present invention generally relate to nanoscale wire devices and methods for use in determining analytes suspected to be present in a sample.

BACKGROUND

Interest in nanotechnology, in particular sub-microelectronic technologies such as semiconductor quantum dots and nanowires, has been motivated by the challenges of chemistry and physics at the nanoscale, and by the prospect of utilizing these structures in electronic and related devices. Nanoscopic articles might be well-suited for transport of charge carriers and excitons (e.g. electrons, electron pairs, etc.) and thus may be useful as building blocks in nanoscale electronics applications. Nanowires are well-suited for efficient transport of charge carriers and excitons, and thus are expected to be important building blocks for nanoscale electronics and optoelectronics.

Nanoscale wires having selectively functionalized surfaces have been described in U.S. Patent Application Serial No. 10/020,004, entitled "Nanosensors," filed December 11, 2001, published as Publication No. 2002/0117659 on August 29, 2002, and as corresponding International Patent Application Serial No. PCT/US01/48230, filed December 11, 2001, published as International Patent Application Publication WO 02/48701 on June 20, 2002 (each incorporated herein by reference). Nanoscale wire sensors have also been described in U.S. Patent Application Serial No. 11/501,466, entitled "Nanoscale Sensors," filed August 9, 2006, also incorporated herein by reference. As described, functionalization of the nanoscale wire may permit interaction of the functionalized nanoscale wire with various entities, such as molecular entities, and the interaction induces a change in a property of the functionalized nanowire, which provides a mechanism for a nanoscale sensor device for detecting the presence or absence of an analyte suspected to be present in a sample.

SUMMARY OF THE INVENTION

Various aspects of the present invention generally relate to nanoscale wire devices and methods for use in determining analytes suspected to be present in a sample. The subject matter of the present invention involves, in some cases, interrelated products, alternative solutions to a particular problem, and/or a plurality of different uses of one or more systems and/or articles.

In one aspect, the invention is directed to a method. In one set of embodiments, the methods includes an act of exposing a nanoscale wire, having a reaction entity immobilized relative thereto, to a solution suspected of containing an analyte that the reaction entity is able to bind. In some cases, the nanoscale wire has a Debye screening length, when the nanoscale wire is placed in the solution, that is greater than the average cross-sectional dimension of the nanoscale wire. In certain instances, the method also includes an act of operating the nanoscale wire under conditions wherein the nanoscale wire has a conductance that is not linearly proportional to voltage applied to voltage applied to the nanoscale wire.

The method, in another set of embodiments, includes acts of causing an analyte to bind to a nanoscale wire having a reaction entity immobilized relative thereto, and determining a change in charge of the analyte of less than about 10^{-17} C.

The invention is directed to an article in another aspect. In one set of embodiments, the article includes a nanoscale wire, having a reaction entity immobilized relative thereto, where the nanoscale wire is exposed to a solution, such that the nanoscale wire has a Debye screening length in the solution that is greater than the average cross-sectional dimension of the nanoscale wire.

In another set of embodiments, the article includes a nanoscale wire, having a reaction entity immobilized relative thereto, where the nanoscale wire can determine a change in charge of an analyte of less than about 10^{-17} C.

In another aspect, the present invention is directed to a method of making one or more of the embodiments described herein, for example, a sensing device comprising a nanoscale wire. In yet another aspect, the present invention is directed to a method of using one or more of the embodiments described herein, for example, a sensing device comprising a nanoscale wire.

Other advantages and novel features of the present invention will become apparent from the following detailed description of various non-limiting embodiments of the invention when considered in conjunction with the accompanying figures. In cases where the present specification and a document incorporated by reference include conflicting and/or inconsistent disclosure, the present specification shall control. If two or more documents incorporated by reference include conflicting and/or inconsistent disclosure with respect to each other, then the document having the later effective date shall control.

BRIEF DESCRIPTION OF THE DRAWINGS

Non-limiting embodiments of the present invention will be described by way of example with reference to the accompanying figures, which are schematic and are not intended to be drawn to scale. In the figures, each identical or nearly identical component illustrated is typically represented by a single numeral. For purposes of clarity, not every component is labeled in every figure, nor is every component of each embodiment of the invention shown where illustration is not necessary to allow those of ordinary skill in the art to understand the invention. In the figures:

Fig. 1 shows the screening effect of a nanoscale wire used as a sensor, in one embodiment of the invention;

Figs. 2A-2D illustrates pH sensing, according to another embodiment of the invention;

Figs. 3A-3D illustrates sensing of PSA/antibody conjugates, in yet another embodiment of the invention;

Figs. 4A-4F illustrate sensing of PSA/antibody conjugates, in still another embodiment of the invention; and

Fig. 5 shows the potential distribution of a nanoscale wire, according to yet another embodiment of the invention.

DETAILED DESCRIPTION

Various aspects of the present invention generally relate to nanoscale wire devices and methods for use in determining analytes suspected to be present in a sample. One aspect of the invention provides a nanoscale wire that has improved sensitivity, for example, as the carrier concentration in the wire is controlled by an external gate voltage, and in some embodiments, the nanoscale wire can be used to determine a change in

charge of less than about 10^{-17} C. The nanoscale wire, in some cases, may be part of a field effect transistor (FET). In one set of embodiments, the nanoscale wire has a Debye screening length that is greater than the average cross-sectional dimension of the nanoscale wire when the nanoscale wire is exposed to a solution suspected of containing an analyte. In certain instances, the Debye screening length associated with the carriers inside nanoscale wire may be adjusted by adjusting the voltage, for example, a gate voltage applied to an FET structure. In some cases, the nanoscale wire can be operated under conditions where the carriers in the nanoscale wire are depleted and the nanoscale wire has a conductance that is not linearly proportional to the voltage applied to the nanoscale wire sensor device, for example, via a gate electrode. Other aspects of the invention include assays, sensors, kits, and/or other devices that include such nanoscale wires, methods of making and/or using functionalized nanoscale wires (for example, in drug screening or high-throughput screening), and the like.

In general, various aspects of the present invention provide a sensing element comprising a nanoscale wire able to interact with one or more analytes. For example, the nanoscale wire may be used to determine an analyte as part of an assay for determining or diagnosing cancer or other medical conditions (e.g., by determining a suitable marker, for example, a hormone, an enzyme, a peptide, a virus, etc., and diagnosing the cancer or other medical condition based on the determination of the marker), for determining drugs (e.g., as part of a drug assay or a drug screen, for instance, to identify a drug able to treat a medical condition such as cancer or aging), for determining toxins or other environmental agents (e.g., by determining binding of the toxin to a receptor), or the like.

Although the invention is generally described herein in reference to a nanoscale wire, it should be understood that the invention is not limited to nanoscale wires. Many of the methods described herein can be applied to any nanomaterials or nanostructures whose properties are affected by the binding of analyte molecules on the surface. As a non-limiting example, the methods of the present invention may be applied to a FET sensor device comprising nanoparticles that an analyte is able to bind. For instance, a nanoparticle (or other nanostructure) may be exposed to a solution such that the nanoparticle has a Debye screening length, when the nanoparticle is placed in the solution, that is greater than the average cross-sectional dimension of the nanoparticle or

partner of the analyte. In some cases, the reaction entity can form a coating on the nanoscale wire. Non-limiting examples of reaction entities include a nucleic acid (e.g.,

DNA or RNA), an antibody, a sugar or a carbohydrate, a protein or an enzyme, a ganglioside or a surfactant, etc., e.g., as discussed herein.

In one set of embodiments, a reaction entity associated with the nanoscale wire is able to interact with an analyte. The reaction entity, as "associated" with or "immobilized" relative to the nanoscale wire, may be positioned in relation to the nanoscale wire (e.g., in close proximity or in contact) such that the analyte can be determined by determining a change in a characteristic or property of the nanoscale wire. Interaction of the analyte with the reaction entity may cause a detectable change or modulation in a property of the nanoscale wire, for example, through electrical coupling with the reaction entity. The term "electrically coupled" or "electrocoupling," when used with reference to a nanoscale wire and an analyte, or other moiety such as a reaction entity, refers to an association between any of the analyte, other moiety, and the nanoscale wire such that electrons can move from one to the other, or in which a change in an electrical characteristic of one can be determined by the other. This can include electron flow between these entities, or a change in a state of charge, oxidation, or the like, that can be determined by the nanoscale wire. As examples, electrical coupling or immobilization can include direct covalent linkage between the analyte or other moiety and the nanoscale wire, indirect covalent coupling (for instance, via a linker, and/or a plurality of linkers, e.g., serially), direct or indirect ionic bonding between the analyte (or other moiety) and the nanoscale wire, direct or indirect bonding of both the analyte and the nanoscale wire to a particle (i.e., the particle acts as a linker between the analyte and the nanoscale wire), direct or indirect bonding of both the analyte and the nanoscale wire to a common surface (i.e., the surface acts as a linker), or other types of bonding or interactions (e.g. hydrophobic interactions or hydrogen bonding). In some cases, no actual covalent bonding is required; for example, the analyte or other moiety may simply be contacted with the nanoscale wire surface. There also need not necessarily be any contact between the nanoscale wire and the analyte or other moiety where the nanoscale wire is sufficiently close to the analyte to permit electron tunneling between the analyte and the nanoscale wire.

Thus, the reaction entity may be positioned relative to the nanoscale wire to cause a detectable change in the nanoscale wire. In some cases, the reaction entity may be positioned within about 100 nm of the nanoscale wire, within about 75 nm of the

nanoscale wire, within about 50 nm of the nanoscale wire, within about 20 nm of the nanoscale wire, within about 15 nm of the nanoscale wire, or within about 10 nm of the nanoscale wire. The actual proximity can be determined by those of ordinary skill in the art. In some cases, the reaction entity is positioned less than about 5 nm from the nanoscale wire. In other cases, the reaction entity is positioned within about 4 nm, within about 3 nm, within about 2 nm, or within about 1 nm of the nanoscale wire.

In some embodiments, the reaction entity is fastened to or directly bonded (e.g., covalently) to the nanoscale wire, e.g., as further described herein. However, in other embodiments, the reaction entity is not directly bonded to the nanoscale wire, but is otherwise immobilized relative to the nanoscale wire, i.e., the reaction entity is indirectly immobilized relative to the nanoscale wire. For instance, the reaction entity may be attached to the nanoscale wire through a linker, i.e., a species (or plurality of species) to which the reaction entity and the nanoscale wire are each immobilized relative thereto, e.g., covalently or non-covalently bound to. As an example, a linker may be directly bonded to the nanoscale wire, and the reaction entity may be directly bonded to the linker, or the reaction entity may not be directly bonded to the linker, but immobilized relative to the linker, e.g., through the use of non-covalent bonds such as hydrogen bonding (e.g., as in complementary nucleic acid-nucleic acid interactions), hydrophobic interactions (e.g., between hydrocarbon chains), entropic interactions, or the like. The linker may or may not be directly bonded (e.g., covalently) to the nanoscale wire.

In one set of embodiments, the sensitivity of the reaction entity to the analyte may be enhanced by selecting conditions in which the Debye screening length of the nanoscale wire is controlled such that the Debye screening length is greater than the average cross-sectional dimension of the nanoscale wire when the nanoscale wire is exposed to a solution suspected of containing the analyte. The Debye screening length can be measured by those of ordinary skill in the art (see, e.g., the examples), and varies as a function of various properties of both the nanoscale wire (e.g., the doping level and/or the dielectric constant) and the environment in which the nanoscale wire is located (e.g., the temperature of the solution).

The Debye length of the nanoscale wire, in some embodiments, can be determined as:

$$\lambda = \sqrt{\varepsilon \, k_B T / pe^2}$$

where ε is the electric constant of wire material, p is the carrier concentration in the nanowire, k_B is the Boltzmann constant (sometimes also k), T is the temperature, and e is the elementary charge. The Debye length of nanoscale wire can be adjusted in some cases by controlling the voltage of the nanoscale wire, e.g., in the gate of a FET comprising the nanoscale wire, which may change the carrier concentration inside wire. In some embodiments, the Debye length may be controlled to be longer than the cross-sectional dimension of the nanoscale wire.

In some embodiments, the Debye screening length (more formally, the Debye-Huckel screening length) of the electrolyte solution is given by:

$$\lambda_D = \sqrt{\frac{\varepsilon_0 \varepsilon_r kT}{2N_A e^2 I}},$$

where I is the ionic strength of the electrolyte, ε_0 is the permittivity of free space, ε_r is the dielectric constant of the solution, k is the Boltzmann constant, T is the temperature, N_A is Avogadro's Number, and e is the elementary charge. Those of ordinary skill in the art will be able to determine these values. Additionally, those of ordinary skill in the art will be able to select suitable environmental conditions (e.g., temperature and/or ionic strength of a given solution) to make the Debye-Huckel screening length of the solution longer, thereby increasing the sensitivity of the nanoscale wire. For instance, the screening length may be greater than the average cross-sectional dimension of the nanoscale wire. For example, the ionic strength of a solution may be controlled by controlling the concentration of phosphate and/or other ions (e.g., K^+, Cl^-, etc.) within the solution.

In another set of embodiments, the sensitivity of the reaction entity to the analyte may be enhanced by operating the nanoscale wire under conditions wherein the nanoscale wire has a conductance that is not linearly proportional to voltage applied to voltage applied to the nanoscale wire, i.e., within the "subthreshold regime." Typically,

the conductance will depend substantially exponentially on the voltage applied to the nanoscale wire, e.g., the electrolyte gate voltage if the nanoscale wire is part of an FET.

Operating the nanoscale wire sensor under conditions such as those described above may yield increased sensitivity. For example, in some cases, the nanoscale wire can be used to determine a change in charge of an analyte of less than about 10^{-17} C, and in some cases, less than about $5x10^{-18}$ C, less than about $3x\ 10^{-18}$ C, less than about 10^{-18} C, or less than about $5x10^{-19}$ C.

In another aspect, the present invention generally relates to the attachment of reaction entities, such as biological entities, to the surfaces of nanoscale wires, in some cases by using covalent bonding. The entity is thus immobilized with respect to the surface of the nanoscale wire. In some embodiments, a linker is used to covalently immobilize the entity with respect to the nanoscale wire. In some cases, the entity may be covalently immobilized with respect to the surface of the nanoscale wire at relatively short distances, depending on the size of the linker and/or the precursors thereof. For instance, the entity may be immobilized at a distance of less than about 20 nm, less than about 15 nm, less than about 10 nm, less than about 9 nm, less than about 8 nm, less than about 7 nm, less than about 6 nm, less than about 5 nm, less than about 4 nm, less than about 3 nm, less than about 2 nm, or less than about 1 nm from the surface of the nanoscale wire. In some cases, the proximity of the entity may control or otherwise affect electronic and/or other properties of the nanoscale wire, for example, the conductivity of the nanoscale wire.

Non-limiting examples of chemistries suitable for attaching entities to surfaces of nanoscale wires, optionally via one or more linkers, include the following. In one set of embodiments of the present invention, the surface of the nanoscale wire may be functionalized, for example, the surface may be functionalized with aldehydes, amines, thiols, or the like, which may form nitrogen-containing or sulfur-containing covalent bonds. For instance, in some embodiments, the reaction entity may be covalently bound to the nanoscale wire through the use of a moiety such as an aldehyde moiety, an amine moiety, and/or a thiol moiety. In certain embodiments, a nanoscale wire may be reacted with an aldehyde, amine, or a thiol in solution to functionalize the nanoscale wire with the appropriate moiety, e.g., such that the surface of the nanoscale wire includes terminal aldehyde, amine, and/or thiol groups. Additional examples are disclosed in U.S. Patent

Application Serial No. 11/501,466, filed August 9, 2006, entitled "Nanoscale Sensors," by Lieber, *et al.*, incorporated herein by reference.

One or more entities, e.g., reaction entities such as proteins, enzymes, nucleic acids, antibodies, receptors, ligands, etc., may then be reacted with the aldehyde, amine, and/or thiol moieties to covalently bind the entity to the nanoscale wire. In some cases, after the entity has been fastened to the nanoscale wire, the surface of the nanoscale wire, including any unreacted moieties, is then passivated, e.g., blocked with one or more compounds that causes the moieties to become unreactive. Non-limiting examples of such passivating agents include ethanolamine. For example, a solution may be added to the nanowires that includes one or more passivating agents.

Also provided, according to another set of embodiments of the present invention, is a sensing element comprising a nanoscale wire and a detector constructed and arranged to determine a property and/or a change in a property of the nanoscale wire. In some cases, alteration of a property of the nanoscale wire may be indicative of an interaction between a reaction entity and an analyte (e.g., association or dissociation of the reaction entity and the analyte). Where a detector is present, any detector capable of determining a property associated with the nanoscale wire can be used. The property can be electronic, electromagnetic, optical, mechanical, or the like. Examples of electrical or magnetic properties that can be determined include, but are not limited to, voltage, current, conductivity, resistance, impedance, inductance, charge, etc. Examples of optical properties associated with the nanoscale wire include its emission intensity and/or emission wavelength, e.g. where the nanoscale wire is emissive. In some cases, the detector will include a power source and a metering device, for example a voltmeter or an ammeter.

In one embodiment, a conductance (or a change in conductance) less than about 1 nS in a nanoscale wire sensor of the invention can be detected. In another embodiment, a conductance in the range of thousandths of a nS can be detected. In other embodiments, conductances of less than about 10 microsiemens, less than about 1 microsiemen, less than about 100 nS, or less than about 10 nS can be detected. The concentration of a species, or analyte, may be detected from femtomolar concentrations, to nanomolar, micromolar, millimolar, and to molar concentrations and above. By using

fluid, saliva, fluid or other samples from tonsils, lymph nodes, needle biopsies, etc.

A variety of sample sizes, for exposure of a sample to a nanoscale sensor of the invention, can be used in various embodiments. As examples, the sample size used in

As an example, a sample, such as a fluid suspected of containing an analyte that is to be determined, may be presented to a sample exposure region of a sensing element comprising a nanoscale wire. An analyte present in the fluid that is able to bind to the

nanoscale wire and/or a reaction entity immobilized relative to the nanoscale wire may cause a change in a property of the nanoscale wire that is determinable upon binding, e.g. using conventional electronics. If the analyte is not present in the fluid, the relevant property of the nanoscale wire will remain unchanged, and the detector will measure no significant change. Thus, according to this particular example, the presence or absence of an analyte can be determined by monitoring changes, or lack thereof, in the property of the nanoscale wire. In some cases, if the detector measures a change, the magnitude of the change may be a function of the concentration of the analyte, and/or a function of some other relevant property of the analyte (e.g., charge or size, etc.). Thus, by determining the change in the property of the nanoscale wire, the concentration or other property of the analyte in the sample may be determined.

In some embodiments, one or more nanoscale wires may be positioned in a channel or in a microfluidic channel, which may define the sample exposure region in some cases. As used herein, a "channel" is a conduit that is able to transport one or more fluids specifically from one location to another. Materials may flow through the channels, continuously, randomly, intermittently, etc. The channel may be a closed channel, or a channel that is open, for example, open to the external environment. The channel can include characteristics that facilitate control over fluid transport, e.g., structural characteristics, physical/chemical characteristics (e.g., hydrophobicity vs. hydrophilicity) and/or other characteristics that can exert a force (e.g., a containing force) on a fluid when within the channel. The fluid within the channel may partially or completely fill the channel. In some cases the fluid may be held or confined within the channel or a portion of the channel in some fashion, for example, using surface tension (i.e., such that the fluid is held within the channel within a meniscus, such as a concave or convex meniscus). The channel may have any suitable cross-sectional shape that allows for fluid transport, for example, a square channel, a circular channel, a rounded channel, a rectangular channel (e.g., having any aspect ratio), a triangular channel, an irregular channel, etc. The channel may be of any size. For example, the channel may have a largest dimension perpendicular to a direction of fluid flow within the channel of less than about 1000 micrometers in some cases (i.e., a microfluidic channel), less than about 500 micrometers in other cases, less than about 400 micrometers in other cases, less than about 300 micrometers in other cases, less than about 200 micrometers in still

and/or the same reaction entities at different concentrations, thereby varying the sensitivity of the nanoscale wires to the analytes, as needed. For example, different reaction entities may be "printed" on the nanoscale wires, e.g., using microarray printing

techniques or the like, thereby producing an array of nanoscale wires comprising different reaction entities. In some cases, individual nanoscale wires may be selected based on their ability to interact with specific analytes, thereby allowing the detection of a variety of analytes. The plurality of nanoscale wires may be randomly oriented or parallel to one another, according to another set of embodiments. The plurality of nanoscale wires may also be oriented in an array on a substrate, in specific instances.

A sensing element of the present invention can collect real time data and/or near-real time data, in some embodiments. The data may be used, for example, to monitor the reaction rate of a specific chemical or biological reaction. Physiological conditions or drug concentrations present *in vivo* may also produce a real time (or near-real time) signal that may be used to control a drug delivery system, in another embodiment of the invention. In addition, electrical determination of one or more properties of the nanoscale wire may allow for the determination of one or more analytes as a function of time. For example, the conductance of a nanoscale wire may be determined as a function of time, which may give additional information regarding the analyte.

In some cases, the nanoscale wires, or at least a portion of the nanoscale wires, may be individually addressable, i.e., the status of the nanoscale wire may be determined without determining the status of nearby nanoscale wires. Thus, for example, a nanoscale wire within a sensing element, or a number of nanoscale wires within the sensing element, may be in electrical communication with an electrode that is able to address the nanoscale wire(s), and such a wire may be addressed using the electrode without addressing other nanoscale wires not in electrical communication with the electrode. For example, a first reaction entity immobilized relative to a first nanoscale wire may bind an analyte, and such a binding event may be detectable independently of the detection of a binding event involving a second reaction entity immobilized relative to a second nanoscale wire. The electrodes may be in electronic communication with one or more electrical contacts.

In some embodiments, the invention includes a microarray including a plurality of sensing regions, at least some of which comprise one or more nanoscale wires. The microarray, including some or all of the sensing regions, may define a sensing element in a sensor device. At least some of the nanoscale wires are able to determine an analyte suspected to be present in a sample that the sensing region of the microarray is exposed

some aspects, any of the techniques described herein may be used in the determination of proteins, enzymes, toxins, viruses, small molecules, or the like, e.g., as in an assay, for example, to detect or diagnose cancer or other medical conditions, toxins or other

environmental agents, viruses, or the like. A property of an analyte may be determined by allowing the analyte to interact with a nanoscale wire and/or a reaction entity, and the interaction may be analyzed or determined in some fashion, e.g., quantified. In some cases, the degree or amount of interaction (e.g., a binding constant) may be determined, for example, by measuring a property of the nanoscale wire (e.g., an electronic property, such as the conductance) after exposing the nanoscale wire and/or the reaction entity to the analyte.

In certain instances, such assays are useful in drug screening techniques. In one example, a protein, enzyme, or other target molecule may be immobilized relative to a nanoscale wire as a reaction entity, and exposed to one or more drug candidates, for example, serially or simultaneously. Interaction of the drug candidate(s) with the reaction entity may be determined by determining a property of the nanoscale wire, e.g., as previously described. As a non-limiting example, a nanoscale wire, having an associated reaction entity, may be exposed to one or more species able to interact with the reaction entity, for instance, the nanoscale wire may be exposed to a sample containing a first species able to interact with the reaction entity, where the sample contains or is suspected of containing a second species able to interact with the reaction entity, and optionally other, different species, where one of the species is a drug candidate. As one example, if the reaction entity is an enzyme, the sample may contain a substrate and a drug candidate suspected of interacting with the enzyme in a way that inhibits enzyme/substrate interaction; if the reaction entity is a substrate, the sample may contain an enzyme and a drug candidate suspected of interacting with the substrate in an inhibitory manner; if the reaction entity is a nucleic acid, the sample may contain an enzyme able to bind the nucleic acid (e.g., a nucleic acid synthesis enzyme), or a complementary nucleic acid, and a drug candidate suspected of interacting with the nucleic acid reaction entity in an inhibitory manner; if the reaction entity is a receptor, the sample may contain a ligand for the receptor and a drug candidate suspected of interacting with the receptor in an inhibitory manner; etc. In each of these cases, the drug candidate may also act in a way that enhances, rather than inhibits, interaction.

In some cases, assays of the invention may be used in high-throughput screening applications, e.g., where at least 100, at least 1,000, at least 10,000, or at least 100,000 or more analytes may be rapidly screened, for example, by exposing one or more analytes

doping, etching, etc. An "individual" or a "free-standing" article is one that can be (but need not be) removed from the location where it is made, as an individual article, and transported to a different location and combined with different components to make a

CuF, CuCl, CuBr, CuI, AgF, AgCl, AgBr, AgI, or the like. Other dopant mixtures may include different mixtures of these elements, such as $BeSiN_2$, $CaCN_2$, $ZnGeP_2$, $CdSnAs_2$,

substantially throughout the crystalline lattice of the article, as opposed to an article in which a dopant is only incorporated in particular regions of the crystal lattice at the atomic scale, for example, only on the surface or exterior. For example, some articles

such as carbon nanotubes are typically doped after the base material is grown, and thus the dopant only extends a finite distance from the surface or exterior into the interior of the crystalline lattice. It should be understood that "bulk-doped" does not define or reflect a concentration or amount of doping in a semiconductor, nor does it necessarily indicate that the doping is uniform. In particular, in some embodiments, a bulk-doped semiconductor may comprise two or more bulk-doped regions. Thus, as used herein to describe nanoscopic wires, "doped" refers to bulk-doped nanoscopic wires, and, accordingly, a "doped nanoscopic (or nanoscale) wire" is a bulk-doped nanoscopic wire. "Heavily doped" and "lightly doped" are terms the meanings of which are understood by those of ordinary skill in the art.

In one set of embodiments, the invention includes a nanoscale wire (or other nanostructured material) that is a single crystal. As used herein, a "single crystal" item (e.g., a semiconductor) is an item that has covalent bonding, ionic bonding, or a combination thereof throughout the item. Such a single-crystal item may include defects in the crystal, but is to be distinguished from an item that includes one or more crystals, not ionically or covalently bonded, but merely in close proximity to one another.

In yet another set of embodiments, the nanoscale wire (or other nanostructured material) may comprise two or more regions having different compositions. Each region of the nanoscale wire may have any shape or dimension, and these can be the same or different between regions. For example, a region may have a smallest dimension of less than 1 micron, less than 100 nm, less than 10 nm, or less than 1 nm. In some cases, one or more regions may be a single monolayer of atoms (i.e., "delta-doping"). In certain cases, the region may be less than a single monolayer thick (for example, if some of the atoms within the monolayer are absent).

The two or more regions may be longitudinally arranged relative to each other, and/or radially arranged (e.g., as in a core/shell arrangement) within the nanoscale wire. As one example, the nanoscale wire may have multiple regions of semiconductor materials arranged longitudinally. In another example, a nanoscale wire may have two regions having different compositions arranged longitudinally, surrounded by a third region or several regions, each having a composition different from that of the other regions. As a specific example, the regions may be arranged in a layered structure within the nanoscale wire, and one or more of the regions may be delta-doped or at least

partially delta-doped. As another example, the nanoscale wire may have a series of regions positioned both longitudinally and radially relative to each other. The arrangement can include a core that differs in composition along its length (changes in composition or concentration longitudinally), while the lateral (radial) dimensions of the core do, or do not, change over the portion of the length differing in composition. The shell portions can be adjacent each other (contacting each other, or defining a change in composition or concentration of a unitary shell structure longitudinally), or can be separated from each other by, for example, air, an insulator, a fluid, or an auxiliary, non-nanoscale wire component. The shell portions can be positioned directly on the core, or can be separated from the core by one or more intermediate shells portions that can themselves be constant in composition longitudinally, or varying in composition longitudinally, i.e., the invention allows the provision of any combination of a nanowire core and any number of radially-positioned shells (e.g., concentric shells), where the core and/or any shells can vary in composition and/or concentration longitudinally, any shell sections can be spaced from any other shell sections longitudinally, and different numbers of shells can be provided at different locations longitudinally along the structure.

In still another set of embodiments, a nanoscale wire may be positioned proximate the surface of a substrate, i.e., the nanoscale wire may be positioned within about 50 nm, about 25 nm, about 10 nm, or about 5 nm of the substrate. In some cases, the proximate nanoscale wire may contact at least a portion of the substrate. In one embodiment, the substrate comprises a semiconductor and/or a metal. Non-limiting examples include Si, Ge, GaAs, etc. Other suitable semiconductors and/or metals are described above with reference to nanoscale wires. In certain embodiments, the substrate may comprise a nonmetal/nonsemiconductor material, for example, a glass, a plastic or a polymer, a gel, a thin film, etc. Non-limiting examples of suitable polymers that may form or be included in the substrate include polyethylene, polypropylene, poly(ethylene terephthalate), polydimethylsiloxane, or the like.

In certain aspects, the present invention provides a method of preparing a nanostructure. In one set of embodiments, the method involves allowing a first material to diffuse into at least part of a second material, optionally creating a new compound. For example, the first and second materials may each be metals or semiconductors, one

controlled growth of the nanoscale wires. In some cases, the nanoscale wire may be doped during growth of the nanoscale wire. Doping the nanoscale wire during growth may result in the property that the doped nanoscale wire is bulk-doped. Furthermore,

desired phase and can continue as long as reactant is available. Growth may terminate when the nanoscale wire passes out of the hot reaction zone and/or when the temperature

In certain cases, a nanoscale wire (or other nanostructure) is formed on the surface of a substrate, and/or is defined by a feature on a substrate. In one example, a nanostructure, such as a nanoscale wire, is formed as follows. A substrate is imprinted

where the position and periodicity control may be achieved by designing specific complementary forces between the patterned surface and the nanoscale wires. Nanoscale wires can also be assembled using a Langmuir-Blodgett (LB) trough. Nanoscale wires

may first be surface-conditioned and dispersed to the surface of a liquid phase to form a Langmuir-Blodgett film. In some cases, the liquid may include a surfactant, which can, in some cases, reduce aggregation of the nanoscale wires and/or reduce the ability of the nanoscale wires to interact with each other. The nanoscale wires can be aligned into different patterns (such as parallel arrays or fibers) by compressing the surface or reducing the surface area of the surface.

Another arrangement involves forming surfaces on a substrate including regions that selectively attract nanoscale wires surrounded by regions that do not selectively attract them. Surfaces can be patterned using known techniques such as electron-beam patterning, "soft-lithography" such as that described in International Patent Application Serial No. PCT/US96/03073, entitled "Microcontact Printing on Surfaces and Derivative Articles," filed March 1, 1996, published as Publication No. WO 96/29629 on July 26, 1996; or U.S. Patent No. 5,512,131, entitled "Formation of Microstamped Patterns on Surfaces and Derivative Articles," issued April 30, 1996, each of which is incorporated herein by reference. Additional techniques are described in U.S. Patent Application Serial No. 60/142,216, entitled "Molecular Wire-Based Devices and Methods of Their Manufacture," filed July 2, 1999, incorporated herein by reference. Fluid flow channels can be created at a size scale advantageous for placement of nanoscale wires on surfaces using a variety of techniques such as those described in International Patent Application Serial No. PCT/US97/04005, entitled "Method of Forming Articles and Patterning Surfaces via Capillary Micromolding," filed March 14, 1997, published as Publication No. WO 97/33737 on September 18, 1997, and incorporated herein by reference. Other techniques include those described in U.S. Patent No. 6,645,432, entitled "Microfluidic Systems Including Three-dimensionally Arrayed Channel Networks," issued November 11, 2003, incorporated herein by reference.

Chemically patterned surfaces other than SAM-derivatized surfaces can be used, and many techniques for chemically patterning surfaces are known. Another example of a chemically patterned surface may be a micro-phase separated block copolymer structure. These structures may provide a stack of dense lamellar phases, where a cut through these phases reveals a series of "lanes" wherein each lane represents a single layer. The assembly of nanoscale wires onto substrate and electrodes can also be assisted using bimolecular recognition in some cases. For example, one biological

binding partner may be immobilized onto the nanoscale wire surface and the other one onto a substrate or an electrode using physical adsorption or covalently linking. An example technique which may be used to direct the assembly of a nanoscopic wires on a substrate is by using "SAMs," or self-assembled monolayers. Any of a variety of substrates and SAM-forming material can be used along with microcontact printing techniques, such as those described in International Patent Application Serial No. PCT/US96/03073, entitled "Microcontact Printing on Surfaces and Derivative Articles," filed March 1, 1996, published as Publication No. WO 96/29629 on July 26, 1996, incorporated herein by reference in its entirety.

In some cases, the nanoscale wire arrays may also be transferred to another substrate, e.g., by using stamping techniques. In certain instances, nanoscale wires may be assembled using complementary interaction, i.e., where one or more complementary chemical, biological, electrostatic, magnetic or optical interactions are used to position one or more nanoscale wires on a substrate. In certain cases, physical patterns may be used to position nanoscale wires proximate a surface. For example, nanoscale wires may be positioned on a substrate using physical patterns, for instance, aligning the nanoscale wires using corner of the surface steps or along trenches on the substrate.

In one aspect, the present invention provides any of the above-mentioned devices packaged in kits, optionally including instructions for use of the devices. As used herein, "instructions" can define a component of instructional utility (e.g., directions, guides, warnings, labels, notes, FAQs ("frequently asked questions"), etc., and typically involve written instructions on or associated with packaging of the invention. Instructions can also include instructional communications in any form (e.g., oral, electronic, digital, optical, visual, etc.), provided in any manner such that a user will clearly recognize that the instructions are to be associated with the device, e.g., as discussed herein. Additionally, the kit may include other components depending on the specific application, for example, containers, adapters, syringes, needles, replacement parts, etc. As used herein, "promoted" includes all methods of doing business including, but not limited to, methods of selling, advertising, assigning, licensing, contracting, instructing, educating, researching, importing, exporting, negotiating, financing, loaning, trading, vending, reselling, distributing, replacing, or the like that can be associated with the methods and compositions of the invention, e.g., as discussed herein. Promoting may

also include, in some cases, seeking approval from a government agency to sell a composition of the invention for medicinal purposes. Methods of promotion can be performed by any party including, but not limited to, businesses (public or private), contractual or sub-contractual agencies, educational institutions such as colleges and universities, research institutions, hospitals or other clinical institutions, governmental agencies, etc. Promotional activities may include instructions or communications of any form (e.g., written, oral, and/or electronic communications, such as, but not limited to, e-mail, telephonic, facsimile, Internet, Web-based, etc.) that are clearly associated with the invention.

Definitions

The following definitions will aid in the understanding of the invention. Certain devices of the invention may include wires or other components of scale commensurate with nanometer-scale wires, which includes nanotubes and nanowires. In some embodiments, however, the invention comprises articles that may be greater than nanometer size (e. g., micrometer-sized). As used herein, "nanoscopic-scale," "nanoscopic," "nanometer-scale," "nanoscale," the "nano-" prefix (for example, as in "nanostructured"), and the like generally refers to elements or articles having widths or diameters of less than about 1 micron, and less than about 100 nm in some cases. In all embodiments, specified widths can be a smallest width (i.e. a width as specified where, at that location, the article can have a larger width in a different dimension), or a largest width (i.e. where, at that location, the article has a width that is no wider than as specified, but can have a length that is greater).

As used herein, a "wire" generally refers to any material having a conductivity of or of similar magnitude to any semiconductor or any metal, and in some embodiments may be used to connect two electronic components such that they are in electronic communication with each other. For example, the terms "electrically conductive" or a "conductor" or an "electrical conductor" when used with reference to a "conducting" wire or a nanoscale wire, refers to the ability of that wire to pass charge. Typically, an electrically conductive nanoscale wire will have a resistivity comparable to that of metal or semiconductor materials, and in some cases, the electrically conductive nanoscale wire may have lower resistivities, for example, resistivities of less than about 100

microOhm cm ($\mu\Omega$ cm). In some cases, the electrically conductive nanoscale wire will have a resistivity lower than about 10^{-3} ohm meters, lower than about 10^{-4} ohm meters, or lower than about 10^{-6} ohm meters or 10^{-7} ohm meters.

A "semiconductor," as used herein, is given its ordinary meaning in the art, i.e., an element having semiconductive or semi-metallic properties (i.e., between metallic and non-metallic properties). An example of a semiconductor is silicon. Other non-limiting examples include gallium, germanium, diamond (carbon), tin, selenium, tellurium, boron, or phosphorous.

A "nanoscopic wire" (also known herein as a "nanoscopic-scale wire" or "nanoscale wire") generally is a wire, that at any point along its length, has at least one cross-sectional dimension and, in some embodiments, two orthogonal cross-sectional dimensions less than 1 micron, less than about 500 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 70, less than about 50 nm, less than about 20 nm, less than about 10 nm, or less than about 5 nm. In other embodiments, the cross-sectional dimension can be less than 2 nm or 1 nm. In one set of embodiments, the nanoscale wire has at least one cross-sectional dimension ranging from 0.5 nm to 100 nm or 200 nm. In some cases, the nanoscale wire is electrically conductive. Where nanoscale wires are described having, for example, a core and an outer region, the above dimensions generally relate to those of the core. The cross-section of a nanoscopic wire may be of any arbitrary shape, including, but not limited to, circular, square, rectangular, annular, polygonal, or elliptical, and may be a regular or an irregular shape. The nanoscale wire may be solid or hollow. A non-limiting list of examples of materials from which nanoscale wires of the invention can be made appears below. Any nanoscale wire can be used in any of the embodiments described herein, including carbon nanotubes, molecular wires (i.e., wires formed of a single molecule), nanorods, nanowires, nanowhiskers, organic or inorganic conductive or semiconducting polymers, and the like, unless otherwise specified. Other conductive or semiconducting elements that may not be molecular wires, but are of various small nanoscopic-scale dimensions, can also be used in some instances, e.g. inorganic structures such as main group and metal atom-based wire-like silicon, transition metal-containing wires, gallium arsenide, gallium nitride, indium phosphide, germanium, cadmium selenide, etc. A wide variety of these and other nanoscale wires can be grown on and/or applied to surfaces in patterns

SWNTs can behave as one-dimensional metals and/or semiconductors. SWNTs. Methods of manufacture of nanotubes, including SWNTs, and characterization are known. Methods of selective functionalization on the ends and/or sides of nanotubes

also are known, and the present invention makes use of these capabilities for molecular electronics in certain embodiments. Multi-walled nanotubes are well known, and can be used as well.

As used herein, an "elongated" article (e.g. a semiconductor or a section thereof) is an article for which, at any point along the longitudinal axis of the article, the ratio of the length of the article to the largest width at that point is greater than 2:1.

A "width" of an article, as used herein, is the distance of a straight line from a point on a perimeter of the article, through the center of the article, to another point on the perimeter of the article. As used herein, a "width" or a "cross-sectional dimension" at a point along a longitudinal axis of an article is the distance along a straight line that passes through the center of a cross-section of the article at that point and connects two points on the perimeter of the cross-section. The "cross-section" at a point along the longitudinal axis of an article is a plane at that point that crosses the article and is orthogonal to the longitudinal axis of the article. The "longitudinal axis" of an article is the axis along the largest dimension of the article. Similarly, a "longitudinal section" of an article is a portion of the article along the longitudinal axis of the article that can have any length greater than zero and less than or equal to the length of the article. Additionally, the "length" of an elongated article is a distance along the longitudinal axis from end to end of the article.

As used herein, a "cylindrical" article is an article having an exterior shaped like a cylinder, but does not define or reflect any properties regarding the interior of the article. In other words, a cylindrical article may have a solid interior, may have a hollowed-out interior, etc. Generally, a cross-section of a cylindrical article appears to be circular or approximately circular, but other cross-sectional shapes are also possible, such as a hexagonal shape. The cross-section may have any arbitrary shape, including, but not limited to, square, rectangular, or elliptical. Regular and irregular shapes are also included.

As used herein, an "array" of articles (e.g., nanoscopic wires) comprises a plurality of the articles, for example, a series of aligned nanoscale wires, which may or may not be in contact with each other. As used herein, a "crossed array" or a "crossbar array" is an array where at least one of the articles contacts either another of the articles or a signal node (e.g., an electrode).

The invention provides, in certain embodiments, a nanoscale wire or wires forming part of a system constructed and arranged to determine an analyte in a sample to which the nanoscale wire(s) is exposed. "Determine," in this context, generally refers to the analysis of a species, for example, quantitatively or qualitatively, and/or the detection of the presence or absence of the species. "Determining" may also refer to the analysis of an interaction between two or more species, for example, quantitatively or qualitatively, and/or by detecting the presence or absence of the interaction, e.g. determination of the binding between two species. As an example, an analyte may cause a determinable change in an electrical property of a nanoscale wire (e.g., electrical conductivity, resistivity, impedance, etc.), a change in an optical property of the nanoscale wire, etc. Examples of determination techniques include, but are not limited to, piezoelectric measurement, electrochemical measurement, electromagnetic measurement, photodetection, mechanical measurement, acoustic measurement, gravimetric measurement, and the like. "Determining" also means detecting or quantifying interaction between species.

A "fluid," as used herein, generally refers to a substance that tends to flow and to conform to the outline of its container. Typically, fluids are materials that are unable to withstand a static shear stress. When a shear stress is applied to a fluid, it experiences a continuing and permanent distortion. Typical fluids include liquids and gases, but may also include free-flowing solid particles, viscoelastic fluids, and the like.

As used herein, a component that is "immobilized relative to" another component either is fastened to the other component or is indirectly fastened to the other component, e.g., by being fastened to a third component to which the other component also is fastened. For example, a first entity is immobilized relative to a second entity if a species fastened to the surface of the first entity attaches to an entity, and a species on the surface of the second entity attaches to the same entity, where the entity can be a single entity, a complex entity of multiple species, another particle, etc. In certain embodiments, a component that is immobilized relative to another component is immobilized using bonds that are stable, for example, in solution or suspension. In some embodiments, non-specific binding of a component to another component, where the components may easily separate due to solvent or thermal effects, is not preferred.

receptor/hormone, receptor/effector, complementary strands of nucleic acid, protein/nucleic acid repressor/inducer, ligand/cell surface receptor, virus/ligand, virus/cell surface receptor, etc.

The term "binding partner" refers to a molecule that can undergo binding with a particular molecule. Biological binding partners are examples. For example, Protein A is a binding partner of the biological molecule IgG, and vice versa. Other non-limiting examples include nucleic acid-nucleic acid binding, nucleic acid-protein binding, protein-protein binding, enzyme-substrate binding, receptor-ligand binding, receptor-hormone binding, antibody-antigen binding, etc. Binding partners include specific, semi-specific, and non-specific binding partners as known to those of ordinary skill in the art. For example, Protein A is usually regarded as a "non-specific" or semi-specific binder. The term "specifically binds," when referring to a binding partner (e.g., protein, nucleic acid, antibody, etc.), refers to a reaction that is determinative of the presence and/or identity of one or other member of the binding pair in a mixture of heterogeneous molecules (e.g., proteins and other biologics). Thus, for example, in the case of a receptor/ligand binding pair the ligand would specifically and/or preferentially select its receptor from a complex mixture of molecules, or vice versa. An enzyme would specifically bind to its substrate, a nucleic acid would specifically bind to its complement, an antibody would specifically bind to its antigen. Other examples include nucleic acids that specifically bind (hybridize) to their complement, antibodies specifically bind to their antigen, binding pairs such as those described above, and the like. The binding may be by one or more of a variety of mechanisms including, but not limited to ionic interactions, and/or covalent interactions, and/or hydrophobic interactions, and/or van der Waals interactions, etc.

The terms "polypeptide," "peptide," and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical analogue of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers. The term also includes variants on the traditional peptide linkage joining the amino acids making up the polypeptide.

As used herein, terms such as "polynucleotide" or "oligonucleotide" or grammatical equivalents generally refer to a polymer of at least two nucleotide bases covalently linked together, which may include, for example, but not limited to, natural nucleosides (e.g., adenosine, thymidine, guanosine, cytidine, uridine, deoxyadenosine, deoxythymidine, deoxyguanosine and deoxycytidine), nucleoside analogs (e.g., 2-

30 those with positive backbones (Denpcy *et al.* (1995) *Proc. Natl. Açad. Sci. USA* 92: 6097; non-ionic backbones (U.S. Patent Nos. 5,386,023, 5,637,684, 5,602,240, 5,216,141 and 4,469,863; Angew. (1991) *Chem. Intl. Ed. English* 30: 423; Letsinger et al. (1988) *J.*

a dimer of Fab which itself is a light chain joined to V_H-C_H1 by a disulfide bond. The F(ab)'2 may be reduced under mild conditions to break the disulfide linkage in the hinge region thereby converting the (Fab')2 dimer into an Fab' monomer. The Fab' monomer

10/196,337, filed July 16, 2002, entitled "Nanoscale Wires and Related Devices," by Lieber, *et al.*, published as U.S. Patent Application Publication No. 2003/0089899 on May 15, 2003; U.S. Patent Application Serial No. 10/720,020, filed November 21, 2003,

sensor prepared in accordance with one embodiment of the invention is shown to be enhanced in the low carrier concentration regime where the screening length is longer than the radius of the nanowire, and therefore the molecules bound on surface can gate

the whole cross-section of nanowire. This is shown by operating a Si-NW FET biosensor in the subthreshold regime with the devices gated in electrolyte. It was shown that the NW FET biosensor operating in the subthreshold regime had high charge sensitivity and a high percentage change in conductance response, which may depend exponentially on the surface potential shift induced by the binding of analyte molecules. This example also shows that optimization of a nanowire FET structure and operating conditions can provide a significant enhancement of, as well as a fundamental understanding for, the sensitivity of a NW-FET sensor. For example, operating in the subthreshold regime was shown in this example to improve the prostate specific antigen (PSA) detection limit down to ~1.5 fM for a NW-FET sensor with a ~0.75 pM detection limit in the linear regime. Also, it may be possible to detect down to as small as several electron charges with the NW FET sensors working in the subthreshold regime, as is shown in this example. These results may have general implications on the sensitivity limits of other FET sensors as well.

For NW biosensors operated as FETs, the sensing mechanism is the field gating effect of charged molecules on the carrier conduction inside NW. Therefore, the highest sensitivity may be achieved when the whole volume of nanodevice is gated by surface charges. This situation may be realized when the carrier screening length is much larger than the radius of the NW, R. Conductance changes of NW FETs can be used to detect pH, proteins, and viruses, for example, as is discussed in U.S. Patent Application Serial No. 11/501,466, filed August 9, 2006, entitled "Nanoscale Sensors," by Lieber, *et al.*, incorporated herein by reference.

Si-NWs used for sensor application often have R on the order of 100 nm, or 10 nm in some cases. In most cases, charged molecules bound on the surface gate the NW within a surface layer of thickness ~1-2 nm. However, at much lower hole densities, p (e.g., lower than $10^{18}/cm^3$), $\lambda_{Si} >> R$ and the whole volume of the NW may be gated by molecules at surface. Thus, there may be a greater response of device and/or an increase in sensor sensitivity under these conditions.

A schematic comparison between these two scenarios is shown in Fig. 1, together with the screening length in silicon plotted as a function of p. This figure shows the screening length effect on the operation and sensitivity of NW FET sensors. The working regime and effectiveness of gating effect induced by molecules at the surface of

the conductance change. Using $\Delta G/G$ to study the sensitivity has a physically meaningful motivation: it is related to the volume ratio between the part of NW that is

gated by surface charges (represented by ΔG) and the whole body of NW (represented by G). Therefore, $\Delta G/G$ is expected to reach maximum when the surface/volume of nano-sensor is fully utilized, which happens when the sensor is near carrier depletion, such that the carrier density is low and $\lambda_{Si} >> R$. Using the above expression for ΔG and $G = e \times \mu \times p \times \pi R^2$ yields the relative conductance response for NW FET sensors in the regime with highest sensitivity ($\lambda_{Si} >> R$) as:

$$\Delta G / G = \exp(-e\Delta\varphi_{Si} / k_B T) - 1. \qquad (1)$$

Although the NW is treated as a three dimensional (3D) system in this derivation, the general approach remains valid when radial confinement makes the system one dimensional (1D), since it only relies on the thermally activated nature of carriers, which follow Boltzmann statistics.

pH sensing experiments were used as a model system to study the sensitivity of NW sensor in the various regimes. Following are nanowire FET fabrication and surface modification for sensing experiments procedures.

Nanowire FET fabrication and electrolyte gating were performed as follows. Silicon nanowires were synthesized by chemical vapor deposition using 10 nm gold nanoparticles as catalysts, with silane as the reactant. Diborane was used during the growth to provide boron as the p-type dopant with a typical B:Si ratio of 1:8000. The FETs were fabricated by photolithography into a patterned array. Nickel (60 nm thick) metal was used as contacts which were passivated/protected from electrolyte by deposition of ~50 nm thick Si_3N_4 after nickel evaporation. The distance between the source-drain electrodes for each FET was 2 μm. pH and PSA samples were delivered to the nanowire devices by a microfluidic channel (with a 500 μm width by 50 μm height cross-section) made of flexible PDMS polymer channel sealed to the device chip. The samples were delivered through inlet/outlet connections in the PDMS polymer by a syringe pump running at typical speed of 0.3 ml/hr. A gold metal pad (without Si_3N_4 passivation) on the chip was used as a global gate electrode for gating all the devices in electrolyte. The FET conductance was measured by a lock-in amplifier at a frequency of 17 Hz and biased voltage of 30 mV.

Nanowire surface modifications were performed as follows. For pH sensing, the silicon nanowire surface was modified with 3-aminopropyltriethoxysilane (3APTS) to provide amino groups at the nanowire surface. The chip was first reacted with 1% 3APTS in ethanol for ~30 min. Then the chip was rinsed with ethanol and baked at 110 °C for 5-10 min before conductance measurements. For PSA sensing (see below), a two-step modification process was used to link antibody receptors to nanowire. Aldehyde groups were first linked to the NW surface by reacting with 1% 3-(trimethoxysilyl)propyl aldehyde (United Chemical Technologies) in ethanol for ~30 min followed by rinsing with ethanol and baking at 110 °C for 10 min. Anti-PSA (AbI, clone ER-PR8, NeoMarkers) was couple to the aldehyde-terminated nanowire surface by reaction of 100 μg/ml antibody in a pH 8.4, 10 mM phosphate buffer solution with 4 mM sodium cyanoborohydride for ~2 h.

In the pH sensing experiments, the silicon oxide (SiO_2) surface of boron doped p-type Si-NW was modified with 3-aminopropyltriethoxysilane. The protonation/deprotonation of amino ($-NH_2$) and silanol (Si-OH) groups changes the surface charge and surface potential of the NW when the pH of electrolyte solution was varied. A gold pad on the chip was used as a gate electrode to gate the NW-FET devices in the electrolyte (inset, Fig. 2A). Fig. 2A shows the conductance G vs. the electrolyte gate voltage V_g of a p-type NW FET. The inset shows a schematic diagram of electrolyte gating. This device has a transconductance ~700 nS/V in the linear regime and a subthreshold slope S~180 mV/decade in the subthreshold regime, with a threshold voltage $V_T \sim 0$ V.

By setting a voltage V_g on gate electrode, a voltage difference V_g was established between the bulk solution and the NW, and the hole concentration in the NW could be tuned. Typically, the devices in this example could be turned on/off within V_g=±0.5V. Fig. 2A shows the $G(V_g)$ curve on a semi-log scale for a NW device with R=5 nm in a pH=7, 10 mM phosphate solution. From the analysis of the NW conductance on surface potential, it can be inferred that the $\lambda_{Si} >> R$ regime was reached in the $G(V_g)$ plot where G depends exponentially on the electrolyte gate voltage V_g, which is called the "subthreshold regime" in semiconductor device physics terminology. The parameter characterizing the FET performance in the subthreshold regime was the subthreshold slope S, which equals the change in V_g needed to tune the device conductance G by a

the potential at the Si/SiO_2 interface of NW, the data were analyzed in terms of $\Delta\varphi_{SiO2}$, the surface potential at the SiO_2/electrolyte interface. The $\Delta G/G$ data at V_g= -0.4 V were

fitted to a linear dependence: $\Delta G/G(pH=4)=g_m \times \Delta\varphi_{SiO2}/G(pH=4)$ with $\Delta\varphi_{SiO2}$ as the only fitting parameter. Using g_m=700 nS/V obtained from the $G(V_g)$ data in electrolyte-gating measurement, $\Delta\varphi_{SiO2} \approx$ -30 mV/pH was obtained. The negative sign comes from the fact that the SiO_2 surface is more negatively charged at higher pH. Below, the pH sensing data were analyzed in the subthreshold regime according to the analysis on the NW sensor response in the $\lambda_{Si} >> R$ regime. To take into account of the potential drop inside SiO_2 layer and the gate coupling efficiency, Eq. 1 was modified to:

$$\Delta G/G = \exp(-\alpha e \Delta\varphi_{SiO2} / k_B T) - 1. \qquad (2)$$

Fitting the V_g= +0.2V data in Fig. 2D to Eq. 2 with the gate coupling efficiency α=1/3, $\Delta\varphi_{SiO2} \approx$ -30 mV/pH was obtained, consistent with the value in the linear regime. The pH sensitivity in terms of surface potential of materials had a theoretical limit of 60 mV/pH, which is set by the Nernst equation. Depending on site densities and the dissociation constants of functional groups on the material surface, the measured $\Delta\varphi$(pH) may be lower than the ideal 60 mV/pH.

EXAMPLE 2

An important advantage of the sensors described herein is their relatively high sensitivity, which may allow purely electrical methods to be used to study analytes such as single biomolecules. This example gives a quantitative calculation of the detected surface charge for a NW sensor with cylindrical geometry, and shows that the subthreshold regime has a low charge detection limit for FET nanosensors. The charge detected for surface potential $\Delta\varphi_{SiO2}$ at the SiO_2/electrolyte interface is given by $Q=C\times\Delta\varphi_{SiO2}$, where C is the capacitance between the surface charge and the NW/electrolyte system. In calculating C, there are three capacitances: the double layer (DL) capacitance C_{DL}, the SiO_2 layer capacitance C_{ox}, and the capacitance of charging NW C_{NW}. When there are surface charges at the SiO_2 surface, carriers in the NW and counter-ions in the electrolyte will come close to the SiO_2 surface to screen out the surface charge. Since surface charge of SiO_2 equals to the net charge in NW plus the charge in the DL of the electrolyte, C can be modeled as C_{DL} in parallel with the series capacitance of C_{ox} and C_{NW}:

$$C = (1/C_{ox}+1/C_{NW})^{-1}+C_{DL}. \qquad (3)$$

Using the double cylinder capacitance formula $2\pi\varepsilon_{SiO2}/\ln(1+d/R)$, C_{ox}= 1.4 $\times 10^{-15}$ F/μm for a typical Si-NW with native SiO_2 thickness d ~1 nm and R=5 nm. The capacitance of the NW, C_{NW}, characterizes how much the chemical potential (or the Fermi energy E_F) of the carriers shifts with respect to the carrier density change: $C_{NW}= e^2 dp/dE_F$. For non-degenerate carriers in NW, the following is derived: $C_{NW} \approx e^2 \times p \times 2\pi R\lambda_{Si}/k_BT$ for $\lambda_{Si}<<R$, and $C_{NW} \approx e^2 \times p \times \pi R^2/k_BT$ for $\lambda_{Si}>>R$ (see below). Note that C_{NW} decreased quickly as the NW was gated from the linear to the subthreshold regime. For instance, C_{NW} drops from ~3×10^{-15} F/μm to ~5×10^{-18} F/μm as p decreased from 1×10^{19}/cm^3 (λ_{Si}~1.5 nm) to 1×10^{16}/cm^3 (λ_{Si}~35 nm). Therefore, in the high p limit, $C \sim C_{ox}+C_{DL}$ and in the low p limit, $C \sim C_{DL}$. By solving the spatial potential distribution inside DL for cylindrical coordinates, the NW-electrolyte DL capacitance was calculated to be $C_{DL} = \pi\varepsilon x K_1(x)/K_0(x)$ (see below), where ε=80 is the dielectric constant of water, $x=R/\lambda$ with λ as the Debye-Huckel screening length of the electrolyte, and $K_0(x)$ and $K_1(x)$ are the zero and first order modified Bessel functions of the second kind. For a 10 mM KCl solution, λ~3 nm and R=5 nm, C_{DL}≈4.7×10^{-15} F/μm. For these parameters, the 2 μm long NW-sensor was estimated to detect $\Delta Q \sim (C_{ox}+C_{DL}) \times 30$ mV/pH = 2300 e/pH in the linear regime, and $\Delta Q \sim C_{DL} \times 30$ mV/pH = 1800 e/pH in the subthreshold regime (e being the elementary charge).

From the above discussion, it can be seen that lower charge detection limit ΔQ_{min}, of the NW sensors could be obtained by reducing C_{NW} and C_{DL}. Thus, better charge sensitivity could be obtained in the subthreshold regime (where $C_{NW} \rightarrow 0$) and in electrolyte with small ionic strength I (as $\lambda \propto I^{-1/2}$). In Table 1, $\Delta Q_{min} = C\Delta\varphi_{min}$ is listed for the sensor shown in Fig. 2. Here, the minimal detectable surface potential shift $\Delta\varphi_{min}$ ~ 5 mV and 0.67 mV in the linear and subthreshold regimes respectively. Also shown are the corresponding ΔQ_{min}, assuming a low ionic strength I=10 μM were used. Table.1 shows that it is possible to detect charge as little as several e using a NW FET sensor working in the subthreshold regime and low ionic strength electrolyte. Besides demonstrating, in this example, the capability of NW FET devices as sensitive charge

A low ionic strength solution (10 μM potassium phosphate + 10 μM KCl, pH~7.4) was used in the PSA sensing experiments to enhance sensitivity. Since PSA molecules have

optimized (in terms of the highest ΔG/G and signal to noise ratio) in the subthreshold

regime, consistent with the above discussion based on the screening length effect on the sensitivity as well as the pH sensing experiments.

Additionally, concentration dependent detection was used to compare the PSA detection limits of the device in the linear vs. subthreshold regime. Real-time conductance sensing data are presented in Figs. 4A-4B to show the detection limit ~0.75 pM for a NW sensor with g_m=2800 nS/V in the linear regime (V_g=0 V). The curves show a minimal PSA detection limit ~0.75 pM for this device in the linear regime. The same device had a subthreshold slope S=100 mV/decade in the subthreshold regime. Figs. 4C-4F show the time dependent conductance measurements for detecting various PSA concentrations (15 pM, 0.75 pM, 37 fM and 1.5 fM) in the subthreshold regime of the same device. These data show that the detection limit of the device improved from ~0.75 pM in the linear regime to ~1.5 fM in the subthreshold regime. Therefore, with Figs. 3 and 4, it can be seen that protein detection in the subthreshold regime of the NW sensor used here has not only a better signal to noise ratio, but a better detection limit.

EXAMPLE 4

To calculate $\Delta\varphi(r)$, the potential profile inside a NW in responding to an adsorbed surface charge of σ (per unit length of NW), one solves the Poisson equation in cylindrical coordinates as:

$$\frac{1}{r}\frac{d}{dr}\left(r\frac{d(\Delta\varphi)}{dr}\right)=-\frac{e}{\varepsilon_{Si}}\Delta p \qquad \text{(S1)}$$

where change in the hole density in NW is $\Delta p(r)= p_i\times\exp[(E_i-e\Delta\varphi-E_F)]/k_BT - p_i\times\exp(E_i-E_F)/k_BT = p\times[\exp(-e\Delta\varphi)/k_BT-1]$.

For a small perturbation ($e\Delta\varphi<<k_BT$), Eq.S1 can be linearized to:

$$\frac{1}{r}\frac{d}{dr}\left(r\frac{d(\Delta\varphi)}{dr}\right)=\frac{pe^2\Delta\varphi}{\varepsilon_{Si}k_BT}=\frac{\Delta\varphi}{\lambda_{Si}^2} \qquad \text{(S2)},$$

with $\lambda_{Si}=\sqrt{\varepsilon_{Si}k_BT/pe^2}$ being the Debye length in silicon with hole density p. The

solution of Eq. S2 for boundary conditions $\Delta\varphi(R) = \Delta\varphi_{Si}$ and $\Delta\varphi(0)$ = finite is:

$$\Delta\varphi(r) = \Delta\varphi_{Si} \times I_0(r/\lambda_{Si}) / I_0(R/\lambda_{Si}) \qquad \text{(S3)}.$$

Here $I_0(x)$ is the zero-order modified Bessel function of the first kind and $\Delta\varphi_{Si}$ is the potential at Si/SiO_2 interface. Eq. S3 is plotted in Fig. 5 at different R/λ_{Si}. It is important to note that for small $x=R/\lambda_{Si} << 1$, $I_0(x) \approx 1$, Eq. S3 physically means that for large λ_{Si} and/or small R, surface charges gate the whole cross-section of NW. For large $x = R/\lambda_{Si} >> 1$, $I_0(x) \approx \frac{e^x}{\sqrt{2\pi x}}$, and the potential falls off quasi-exponentially from the surface of NW within a layer of thickness ~ λ_{Si}. Fig. 5 shows the potential distribution $\Delta\varphi(r)$ inside silicon nanowire at different ratios between the nanowire radius R and the carrier screening length λ_{Si}. $\Delta\varphi(r)$ is normalized by its value at surface.

Following is a discussion of the relationship between surface charge and surface potential. Due to the total charge neutrality of the system:

$$\sigma = -e \times \int_0^R 2\pi r \Delta p(r) dr = e \times \int_0^R 2\pi r \times p \times \{1 - \exp(-e\Delta\varphi / k_B T)\} dr \qquad \text{(S4)}.$$

Solving Eq. S3 and S4 gives how much the surface potential $\Delta\varphi_{Si}$ is for surface charge adsorption of σ.

Now consider two limiting cases: $R << \lambda_{Si}$ (low carrier density) or $R >> \lambda_{Si}$ (high carrier density). For $x = R/\lambda_{Si} << 1$, $I_0(x) = 1 + O(x^2) \approx 1$:

$$\Delta\varphi(r) \approx \Delta\varphi_{Si}$$

For $0 \le r \le R$; Eq. S4 simplifies to:

$$\sigma = e \times \pi R^2 \times p \times \{1 - \exp(-e\Delta\varphi_{Si} / k_B T)\} \qquad \text{(S5)}.$$

Note that although the Poisson equation S1 treats NW as a 3D system, the result of

exponential dependence of σ on $\Delta\varphi_{Si}$ at $R<<\lambda_{Si}$ will not change even if the radial confinement of NW is considered and the system is 1D. This is because, in Eq.S5, the carriers are thermally activated and follow Boltzmann statistics. For the 1D case, one replaces $\pi R^2 \times p$ in Eq.S5 with the 1D charge density per unit length. If a small perturbation is considered ($e\Delta\varphi<<k_BT$), Eq. 4 can be linearized and evaluated:

$$\sigma \approx e \times \int_0^R 2\pi r \times p \times e\Delta\varphi(r)/k_BT dr = p \times 2\pi R\lambda_{Si} \times \frac{e^2\Delta\varphi_{Si}}{k_BT} \times \frac{I_1(R/\lambda_{Si})}{I_0(R/\lambda_{Si})} \qquad \text{(S6)},$$

where $I_1(x)$ is the first-order modified Bessel function of the first kind, and the relationship $dxI_1(x)/dx=xI_0(x)$ is used. For $R/\lambda_{Si}>>1$, Eq. S6 further simplifies to:

$$\sigma \approx p \times 2\pi R\lambda_{Si} \times \frac{e^2\Delta\varphi_{Si}}{k_BT} \qquad \text{(S7)}.$$

By differentiating Eq. S6, the differential capacitance of nanowire is:

$$C_{NW} = \frac{d\sigma}{d\Delta\varphi} \approx \frac{e^2 \times p \times \pi R^2}{k_BT} \times \frac{2\lambda_{Si}}{R} \times \frac{I_1(R/\lambda_{Si})}{I_0(R/\lambda_{Si})} \qquad \text{(S8)}.$$

Eq. S8 gives the charging capacitance of a NW and has the following asymptotic behavior: $C_{NW} \approx e^2 \times p \times 2\pi R\lambda_{Si}/k_BT$ for $\lambda_{Si}<<R$; and $C_{NW} \approx e^2 \times p \times \pi R^2/k_BT$ for $\lambda_{Si}>>R$. Note that Eq. S8 at the $\lambda_{Si}>>R$ limit is consistent with the well known compressibility of a non-degenerate electron gas, and remains valid for 1D after replacing $p \times \pi R^2$ with the 1D charge density (which can be shown to be true by calculating the exact density dependence of the chemical potential of 1D Fermions at finite temperatures). The screening length of silicon enters C_{NW} in the expression at the $\lambda_{Si}<<R$ limit accounts for the fact that the chemical potential of carriers in NW only changes inside a layer of thickness ~ λ_{Si} nearby its surface.

For the capacitance between an electrolyte solution and a nanowire, first, consider the potential distribution in the double layer (DL) formed by electrolyte near

NW surface. The Poisson equation is:

$$\frac{1}{r}\frac{d}{dr}\left(r\frac{d\varphi}{dr}\right)=-\frac{\rho e}{\varepsilon}\exp(-e\varphi/k_BT)+\frac{\rho e}{\varepsilon}\exp(e\varphi/k_BT)=\frac{2\rho e}{\varepsilon}\sinh(e\varphi/k_BT), \qquad (S9)$$

where ρ and ε are the ionic concentration and dielectric constant of the electrolyte. The solution of Eq. S9 for boundary conditions $\varphi(R)=\Delta\varphi$ and $\varphi(\infty)=0$ and small perturbations is:

$$\varphi(r)=\Delta\varphi\times K_0(r/\lambda)/K_0(R/\lambda), \quad \text{and } r\geq R \qquad (S10),$$

where λ is the Debye-Huckel screening length of electrolyte and $K_0(x)$ is the zero-order modified Bessel function of the second kind, which has asymptotic behavior $K_0(x) \approx -\ln(x)$ for $x<<1$. Additionally, $K_0(x)\approx\frac{e^{-x}}{\sqrt{2x/\pi}}$ for $x>>1$. The total charge inside the DL is:

$$\begin{aligned} Q&=\int_R^\infty -\rho\times e\times 2\pi r\times\sinh(e\varphi/k_BT)dr\approx\int_R^\infty -\rho\times e\times 2\pi r\times e\varphi(r)/k_BTdr \\ &=-\frac{\rho e^2 2\pi R\lambda\Delta\varphi}{k_BT}\frac{K_1(R/\lambda)}{K_0(R/\lambda)}=-\pi\varepsilon\Delta\varphi\times\frac{R}{\lambda}\times\frac{K_1(R/\lambda)}{K_0(R/\lambda)} \end{aligned} \qquad (S11)$$

This derivation makes use of the relationship $dxK_1(x)/dx=-xK_0(x)$ and $\lambda^2=\varepsilon k_BT/2\rho e^2$. For an electrolyte with low ionic strength ($R/\lambda=x<<1$): $K_0(x)\sim-\ln(x)$ and $K_1(x)\sim 1/x$, Eq. S11 turns into $Q=\frac{\pi\varepsilon\Delta\varphi}{\ln(R/\lambda)}$. Therefore the capacitance between solution and per unit length of NW is (denote as DL capacitance C_{DL}):

$$\begin{aligned} C_{DL}&=|Q|/\Delta\varphi=\pi\varepsilon\times\frac{R}{\lambda}\times\frac{K_1(R/\lambda)}{K_0(R/\lambda)} \\ &\approx\frac{\pi\varepsilon}{\ln(\lambda/R)};\text{if } R<<\lambda \end{aligned} \qquad (S12),$$

where the asymptotic behavior at small R/λ is a logarithmic dependence, similar to the naïve picture of modeling DL as two cylindrical sheets of charges separated at distance of screening length: $2\pi\varepsilon/\ln(1+\lambda/R)$.

While several embodiments of the present invention have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the present invention. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the teachings of the present invention is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, the invention may be practiced otherwise than as specifically described and claimed. The present invention is directed to each individual feature, system, article, material, kit, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not mutually inconsistent, is included within the scope of the present invention.

All definitions, as defined and used herein, should be understood to control over dictionary definitions, definitions in documents incorporated by reference, and/or ordinary meanings of the defined terms.

The indefinite articles "a" and "an," as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to mean "at least one."

The phrase "and/or," as used herein in the specification and in the claims, should be understood to mean "either or both" of the elements so conjoined, i.e., elements that

as a non-limiting example, "at least one of A and B" (or, equivalently, "at least one of A or B," or, equivalently "at least one of A and/or B") can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally

6. The method of claims 1, 2, or 3, wherein the reaction entity comprises a nucleic acid.

7. The method of claims 1, 2, or 3, wherein the reaction entity comprises a protein.

8. The method of claims 1, 2, or 3, wherein the reaction entity comprises an enzyme.

9. The method of claims 1, 2, or 3, wherein the reaction entity comprises an antibody.

10. The method of claims 1, 2, or 3, wherein the reaction entity is covalently immobilized to the nanoscale wire.

11. The method of claims 1, 2, or 3, wherein the reaction entity is immobilized to the nanoscale wire via a linker.

12. The method of claims 1, 2, or 3, wherein the reaction entity is positioned within 5 nanometers of the nanowire.

13. The method of claims 1, 2, or 3, wherein the reaction entity is positioned within 3 nanometers of the nanowire.

14. The method of claims 1, 2, or 3, wherein the reaction entity is positioned within 1 nanometer of the nanowire.

15. The method of claims 1, 2, or 3, wherein the nanoscale wire is a semiconductor nanowire.

16. The method of claim 15, wherein the semiconductor nanowire is a silicon nanowire.

17. The method of claims 1, 2, or 3, wherein the reaction entity specifically binds the analyte.

18. The method of claims 1, 2, or 3, wherein the reaction entity nonspecifically binds the analyte.

19. The method of claim 3, wherein the nanoscale wire is contained in a solution.

20. The method of claims 1, 2, or 19, wherein the solution has an ionic strength of less than about 10 mM.

21 The method of claims 1, 2, or 19, wherein the solution has an ionic strength of less than about 3 mM.

22 The method of claims 1, 2, or 19, wherein the solution has an ionic strength of less than about 1 mM.

23 The method of claims 1, 2, or 19, wherein the solution has an ionic strength of less than about 300 micromolar.

24 The method of claims 1, 2, or 19, wherein the solution has an ionic strength of less than about 100 micromolar.

25 The method of claims 1, 2, or 19, wherein the solution has an ionic strength of less than about 30 micromolar.

26 The method of claims 1, 2, or 19, wherein the solution has an ionic strength of less than about 10 micromolar.

27. An article, comprising:

a nanoscale wire, having a reaction entity immobilized relative thereto, the nanoscale wire exposed to a solution, wherein the nanoscale wire has a Debye screening length in the solution that is greater than the average cross-sectional dimension of the nanoscale wire.

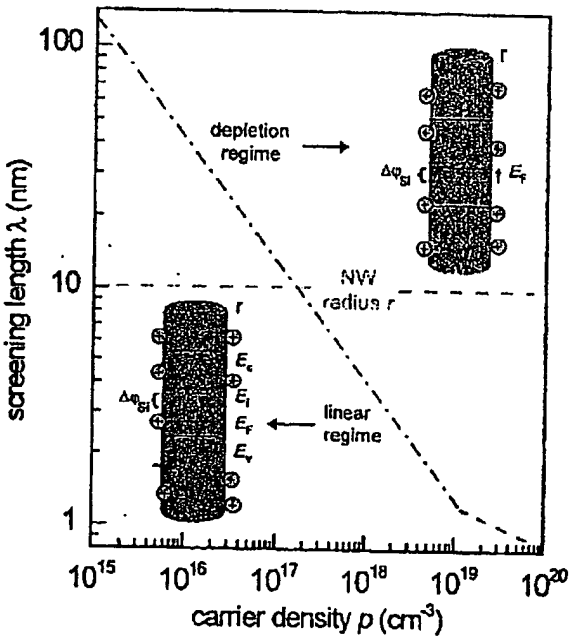
100
10
1
screening length λ (nm)
depletion regime
NW radius r
linear regime
r
E_c
E_i
E_F
E_v
$\Delta\varphi_{SI}$
10^{15}
10^{16}
10^{17}
10^{18}
10^{19}
10^{20}
carrier density p (cm^{-3})

Figure 1

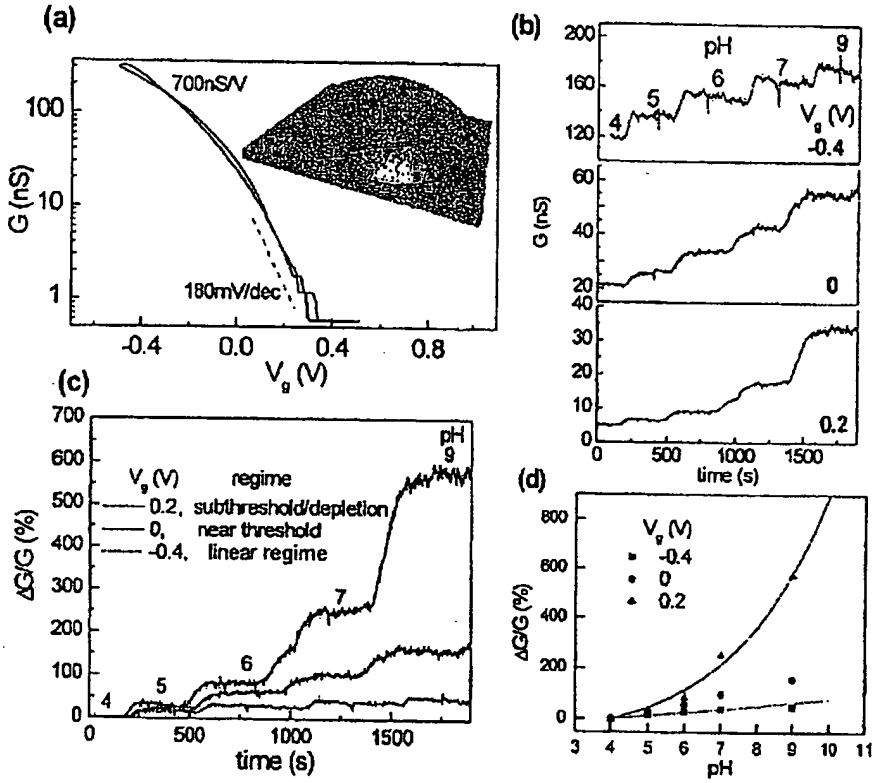
(a)
700nS/V
180mV/dec
G (nS)
V_g (V)
(b)
pH
V_g (V)
-0.4
0
0.2
G (nS)
time (s)
(c)
V_g (V) regime
0.2, subthreshold/depletion
0, near threshold
-0.4, linear regime
ΔG/G (%)
time (s)
(d)
V_g (V)
-0.4
0
0.2
ΔG/G (%)
pH

Figure 2

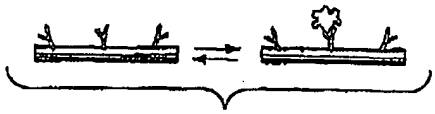

Fig. 3A

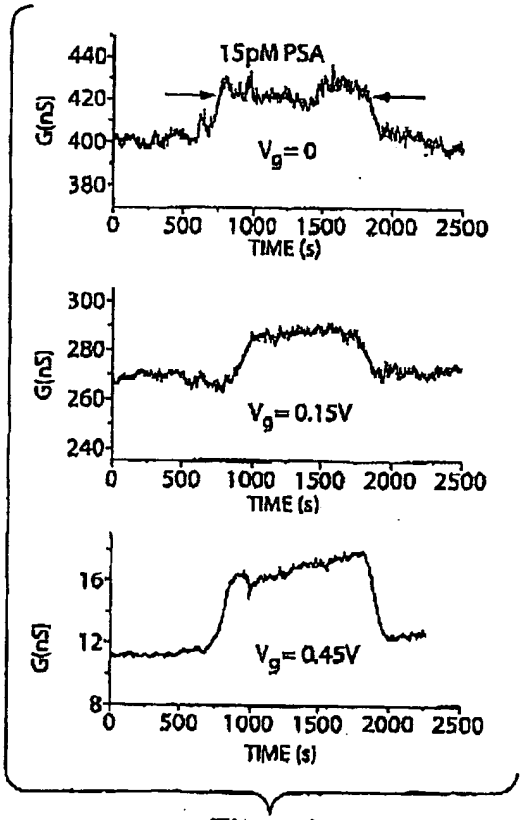
15pM PSA
G(nS)
440
420
400
380
V_g= 0
0 500 1000 1500 2000 2500
TIME (s)
300
280
260
240
V_g= 0.15V
16
12
8
V_g= 0.45V

Fig. 3B

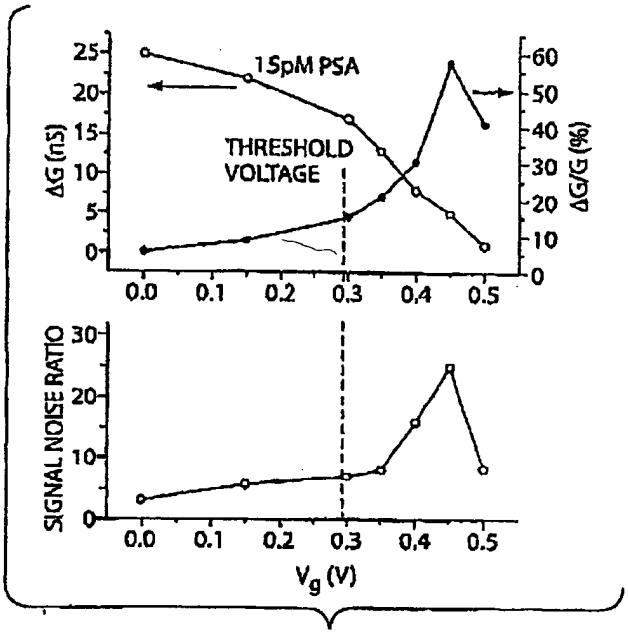
15pM PSA
THRESHOLD VOLTAGE
ΔG (nS)
ΔG/G (%)
SIGNAL NOISE RATIO
V_g (V)

Fig. 3C

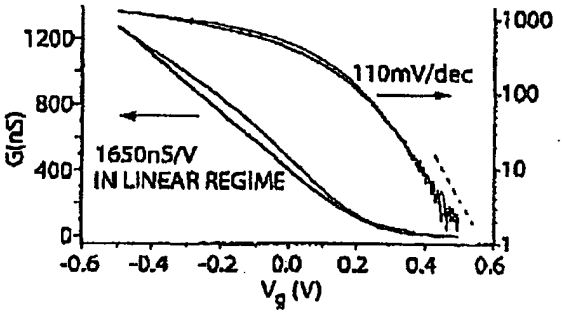
110mV/dec
1650nS/V
IN LINEAR REGIME
G(nS)
V_g (V)

Fig. 3D

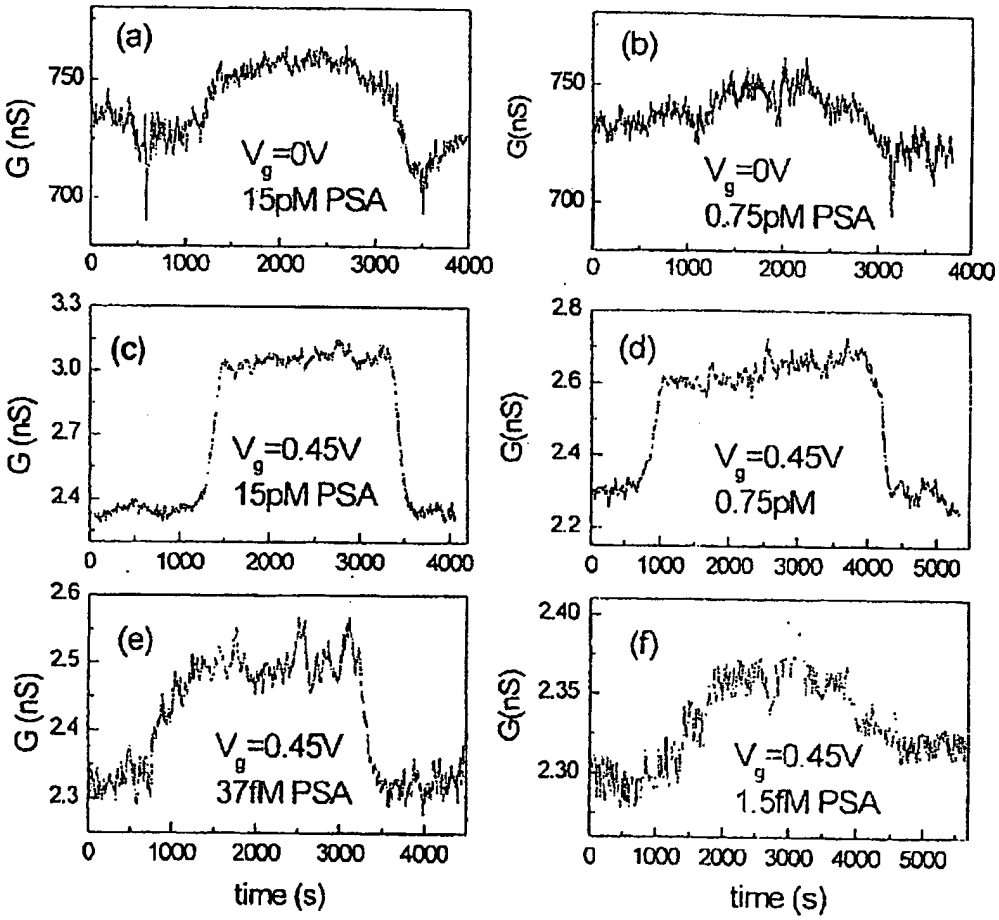
(a)
G (nS)
750
700
V_g=0V
15pM PSA
0
1000
2000
3000
4000
(b)
G(nS)
750
700
V_g=0V
0.75pM PSA
0
1000
2000
3000
4000
(c)
G (nS)
3.3
3.0
2.7
2.4
V_g=0.45V
15pM PSA
0
1000
2000
3000
4000
(d)
G(nS)
2.8
2.6
2.4
2.2
V_g=0.45V
0.75pM
0
1000
2000
3000
4000
5000
(e)
G (nS)
2.6
2.5
2.4
2.3
V_g=0.45V
37fM PSA
0
1000
2000
3000
4000
time (s)
(f)
G(nS)
2.40
2.35
2.30
V_g=0.45V
1.5fM PSA
0
1000
2000
3000
4000
5000
time (s)

Figure 4

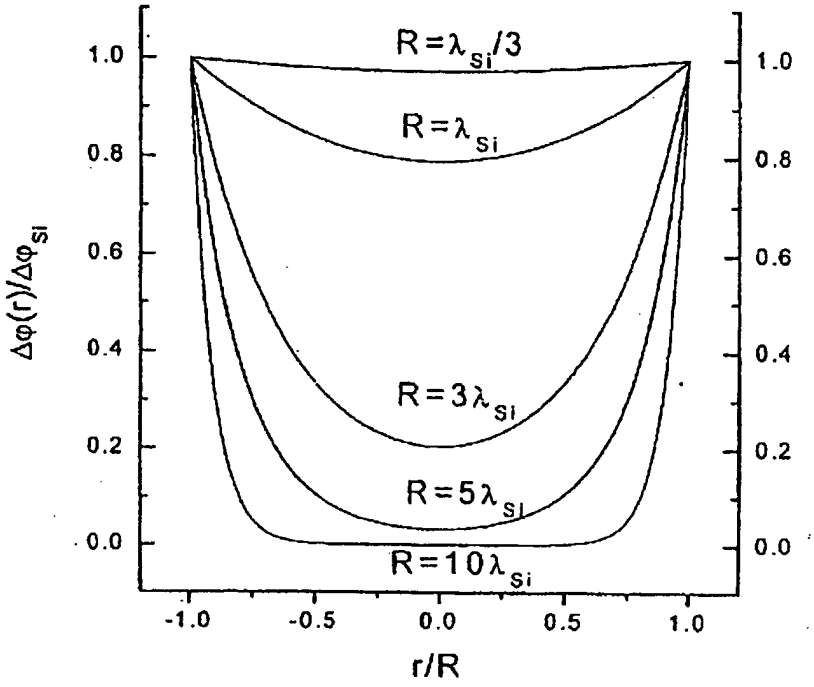
R=λ_Si/3
R=λ_Si
R=3λ_Si
R=5λ_Si
R=10λ_Si
Δφ(r)/Δφ_SI
r/R
1.0
0.8
0.6
0.4
0.2
0.0
-1.0
-0.5
0.0
0.5
1.0

Figure 5.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/024126

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N27/414

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, COMPENDEX, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 2002/117659 A1 (LIEBER CHARLES M [US] ET AL) 29 August 2002 (2002-08-29) cited in the application paragraphs [0063], [0091]; figures 14a,14b	1,2, 6-19,27, 29-32 20-26
X	WANG W U ET AL: "Label-free detection of small-molecule-protein interactions by using nanowire nanosensors" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC.; US, vol. 102, no. 9, 1 March 2005 (2005-03-01), pages 3208-3212, XP002478997 ISSN: 0027-8424	27,29-32
Y	page 3208, right-hand column, paragraph 2 page 3209, right-hand column, paragraph 2	20-26

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 September 2008	02/10/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Wilhelm, Jörg

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/024126

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZHENG G ET AL: "Multiplexed electrical detection of cancer markers with nanowire sensor arrays" NATURE BIOTECHNOLOGY, NATURE PUBLISHING GROUP, NEW YORK, NY, US, vol. 23, no. 10, 1 October 2005 (2005-10-01), pages 1294-1301, XP002414583 ISSN: 1087-0156 page 1299, right-hand column, last paragraph - page 1300, left-hand column, paragraph 4; figures 1-3	27,29-32
X	WO 2006/107312 A (HARVARD COLLEGE [US]; WANG WAYNE [US]; CHEN CHUO [US]; LIN KENG-HUI [U) 12 October 2006 (2006-10-12)	27,29-32
A	page 5, lines 12-20; claims 13-27 page 37, line 3 - page 38, line 20	1,2
A	CUI YI ET AL: "Diameter-controlled synthesis of single-crystal silicon nanowires" APPLIED PHYSICS LETTERS, AIP, AMERICAN INSTITUTE OF PHYSICS, MELVILLE, NY, vol. 78, no. 15, 9 April 2001 (2001-04-09), pages 2214-2216, XP012027731 ISSN: 0003-6951 abstract; figure 2	1,27
A	PATOLSKY FERNANDO ET AL: "Nanowire-based biosensors" ANALYTICAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. COLUMBUS, US, vol. 78, no. 13, 1 July 2006 (2006-07-01), pages 4260-4269, XP002470513 ISSN: 0003-2700 the whole document	6-9

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 3-5,28

Claims 3-5 and 28 do not clearly define any searchable subject-matter, because they relate to methods and products having a given desired effect, namely a very low detection limit, see PCT Guidelines 9.21.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/024126

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 3-5, 28.
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/024126

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002117659 A1	29-08-2002	US 2006054936 A1	16-03-2006
		US 2008211040 A1	04-09-2008
		US 2007158766 A1	12-07-2007
WO 2006107312 A	12-10-2006	US 2007264623 A1	15-11-2007